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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/884,466	06/20/2001	Arthur L. Herbst	58532-012	9630

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EXAMINER
KIM, VICKIE Y

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 04/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/884,466	Applicant(s) HERBST ET AL.	
	Examiner Vickie Kim	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P ri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☒ Claim(s) 5 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Seibert et al (US patent 5,972,986).

Claim 1 reads on a method of reducing one or more deleterious side effect of radiation treatment, comprising administering an effective amount of selective cyclooxygenase(COX)-2 inhibitor.

Seibert et al teach a method of treating fibrosis which occurs with radiation therapy using the selective COX-2 inhibitor (see column 2, lines 59-61 and column 2, lines 1-6). The critical element required by the instant claim (i.e. reducing deleterious side effect) is inherently accomplished when COX-2 inhibitor is used for treating fibrosis that is unwanted result caused by the ratdiation therapy as taught by the Seibert et al. Thus the claimed subject matter is anticipated and not patentably distinct over the prior art of the record.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seibert et al(US patent 5,972,986) .

Claim 3 calls for celecoxib as the selective COX-2 inhibitor.

Seibert et al teach a method of treating fibrosis caused by radiation therapy using selective COX-2 inhibitors including as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide. It is noted that celecoxib's chemical name is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide (see column 2, lines 59-61 and column 1, lines 28-65). Thus it would have been obvious to one of ordinary skill in the art to select celecoxib to treat fibrosis caused by radiation therapy because celecoxib inhibits COX-2 enzyme selectively and celecoxib is particularly preferred species of selective COX-2 inhibitor as suggested in Seibert's reference (see

column 9, lines 51-55). Thus one would have been motivated to do so with reasonable expectation of success.

8. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seibert et al(US patent 5,972,986) in view of Ducharme et al (US patent 5,474,995)

As mentioned in 102 rejection (supra), Seibert et al teach the method of treating side effect which occurs with radiation therapy using selective COX-2 inhibitors.

This claim differs in that a specific COX-2 inhibitor is required, namely rofecoxib.

However, Ducharme et al teach 3-phenyl-4-(4-(methylsulfonyl)phenyl-2-(5H)-furanone as a selective COX-2 inhibitor (see claim 14). It is noted that rofecoxib's chemical name is 3-phenyl-4-(4-(methylsulfonyl)phenyl-2-(5H)-furanone. Thus, it would have been obvious to one of ordinary skill in the art to substitute rofecoxib for any suggested selective COX-2 inhibitors(e.g. celecoxib) in Seibert's patent to achieve same therapeutic effect because they selectively inhibit COX-2 enzyme. Ducharme's patent(US'995) is particularly relevant to Seibert's teaching because each patentee teaches selective COX-2 inhibitors but also Seibert cites Ducharme(US'995) patent as a pertinent reference where numerous compounds having COX-2-selective inhibiting activity are described therein (see Seibert's patent, column 1, line 37).

9. Claims 4-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seibert et al(US patent 5,972,986) in view of Kurakata (EP patent 0927555) and Weichselbaum et al(US patent 5,641,755), if necessary, further in view of Milas et al(J. Nat. Cancer Ins., 1999).

In additional to Siebert's teaching aforementioned in the 102 rejection, Seibert also teaches a conjunctive treatment of a selective COX-2 inhibitor reduces the toxic side effects associated with chemotherapy by reducing the concentration of the side effect-causing agent needed for therapeutic efficacy; see column 2, lines 1-6.

Applicant's claims differ because claims 4-7 and 9 require various side effects (e.g. acute mucosal effect, fatigue, diarrhea, urinary frequency, dermatitis, respectively) and claim 8 requires specific location of the radiation therapy (i.e. outside the pelvis).

However, it would have been obvious to one of ordinary skill in the art to extend Seibert's teaching to reduce mucositis, fatigue, diarrhea, urinary frequency or dermatitis when Seibert is modified in view of Kurakata and Weichselbaum, if necessary, further in view of Milas because the deficiency of Seibert is satisfied when they are taken together.

Firstly, Kurakata teaches that a selective COX-2 inhibitor is potent anti-inflammatory agent and has an inhibitory effect on cytokine production(particularly TNF-α and IL-1) via inhibition of prostaglandin/arachidonic pathway that is responsible for inflammation reaction(see page 1, 9th paragraph).

Secondly, Weichselbaum et al disclose particularly relative teaching regarding radiation-induced side effects (i.e. mucositis, dermatitis or proctitis) and inflammatory cytokines such as tumor necrosis factor(TNF) where inflammatory cytokines are responsible for radiation-induced side effects and inflammatory cytokine production is mediated by prostaglandin/arachidonic metabolic pathway. Weichselbaum states that

radiation-induced side effects could be effectively reduced by the inhibition of said metabolic pathway which attenuates the production of cytokines such as TNF-α.

As to claim 8, Weichselbaum further teaches various radiation exposures to different locations to treat specific tumors (e.g. oropharyngeal mucosa, ultraviolet radiation to skin, etc (see column 7)).

Thus one having ordinary skill in the art would have been motivated to modify Seibert's teaching so as to include further teaching of Kurakata and Weichselbaum wherein one would have been expected the successful result from the utilization of COX-2 inhibitor in mucositis, proctitis, or dermatitis treatment because selective COX-2 inhibitor effectively inhibits prostaglandin production that attenuates inflammatory cytokine production.

Milas teaches the biological effects of prostaglandin and its production via arachidonic pathway. Milas also teaches prostaglandin production inhibition mediated by inhibiting cyclooxygenase enzymes(COX-1 and COX-2), especially selective COX-2 inhibition could be utilized advantageously due to fewer side effects. In addition to that, Milas further teaches enhancement(potentiation) of tumor response to radiation and potential for improving the efficacy of radiotherapy achieved by selective COX-2 inhibitors; see page 1503, last paragraph.

Thus, if necessary, when these references are taken together, one would have been motivated to add selective COX-2 inhibitor into radiation treatment to reduce the deleterious side effects(e.g. dermatitis, mucositis, etc) because selective COX-2 inhibitors are not only modulating prostaglandin/arachidonic pathway, eventually

attenuating inflammatory cytokines(TNF-α or IL-1) production, but also potentiating tumor response to cytotoxic agent such as ionizing radiation as suggested. The possible deleterious side effects associated with radiation therapy could be reduced by lowering the dose of the radiation as suggested in Milas. In other words, treatment requires less radiation to achieve same therapeutic outcome and less side effects are expected.

With respect to claims 5 and 7, they require fatigue and urinary frequency and are properly included in this rejection because it is well known in the art that fatigue or urinary frequency are also radiation induced side effect mediated by prostaglandin pathway involving TNFα and IL-1 induced inflammation evidenced by documents enclosed in PTO-892.

One would have been expected the reasonable success because COX-2 inhibitors are ultimately responsible for attenuation of cytokines production(i.e. TNF-α and IL-1). By lowering the incidence of side effects, one would also have expected an improvement in the quality of the life of a patient and an improvement in patient compliance.

One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same (or similar) ingredients and share common utilities, and pertinent to the problem which applicant is concerning. MPEP 2141.01(a).

Conclusion

10. All the pending claims 1-9 are rejected. No claims allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vickie Kim whose telephone number is (703) 305-1675 (Tuesday-Friday: 8AM-6:30PM).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Vickie Kim,
Patent examiner, Art unit 1614
April 22, 2002